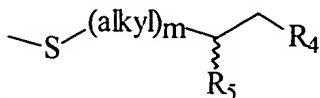


al
Contd
PS
3/03
15. (new) The method of Claim 5 wherein R₁ is lower alkyl, a sulfur-containing amino acid or



REMARKS

Receipt of the Office Action of October 8, 2002 is acknowledged. Reconsideration of Claims 1-13 is respectfully requested in view of the following argument. Favorable consideration is also solicited for new Claims 14 and 15.

Claims 1-13 were initially rejected as obvious over the Morozov et al reference, U.S. Patent 5,770,576. The Examiner has incorrectly applied the limited teachings of Morozov et al, and it is respectfully submitted that no *prima facie* case of obviousness has been presented. To establish a case of *prima facie* obviousness, the Examiner must fulfill three criteria: 1) There must be some suggestion or motivation in the reference or known to those skilled in the art to modify the reference; 2) a reasonable expectation of success; and 3) the prior art must teach each and every claim limitation.

First, contrary to the conclusions of the Examiner, Morozov, et al does not teach or suggest combination therapy for radiation exposure. Applicant has carefully reviewed the Morozov, et al reference, particularly those sections cited by the Examiner. None of these sections, nor any other portion of Morozov, et al, teaches or suggests that mesna (or any other compounds encompassed within the scope of the instant Claims) may be used in combination with any other agent to treat patients for radiation exposure.

Second, with regard to the formula I compounds, only mesna is mentioned and mesna is given passing mention only once in the entire 156 column specification. In fact, the

reference to mesna is an erroneous one in that Morozov, et al, column 20, line 43 to column 21, line 21, refers to mesna in a laundry list of 137 “chemotherapeutic” drugs (some of which are double inclusions). It is well known that mesna is not a chemotherapeutic drug as that term is understood in the medical arts, since mesna possesses little or no antineoplastic activity. Instead, mesna is a well-known protective agent for ifosfamide, an antineoplastic (chemotherapeutic) agent. Further none of agents in the Column 20-21 laundry list (including mesna) is known to possess any efficacy whatsoever as a radiation protector.

Third, Morozov et al does not teach the concept of combination therapy for radiation protection. The suggestions in Morozov et al are that combinations of agents may be used to treat conditions that often arise in conjunction with exposure to radiation (cancers, leukemia, immunodeficiency, infections, etc.). Morozov et al, at columns 20-23 lists hundreds of drug agents as being available for use to treat these secondary conditions, and consists of nothing more than a large laundry list of well-known antibiotics, antifungals, antivirals and antineoplastic drugs, and none of these suggest anything about the use of any combination treatment for radiation exposure.

Only 3 of the 49 Examples in Morozov et al deal with the potential treatment of radiation exposure. None of Examples 2, 3 or 12 in any way teaches the use of combination drug therapy to treat patients exposed to radiation or patients who would be so exposed in the future. These Examples all advocate single agent therapy, with L-Glu-L-Trp as the preferred agent.

Morozov et al broadly teaches use of a single agent administered to a patient, an L-Glu-L-Trp dipeptide, as a treatment for systemic toxicity that results in compromise of the patient’s immune system. Contrary to the Examiner’s statement that, “the treatment regimen may

optionally be combined with a second pharmaceutical agent, to treat exposure to radiation” the cited passages do not teach or even remotely suggest combination drug treatment for radiation exposure.

Column 12, line 60 to Column 13, line 1 teaches nothing, other than reciting a laundry list of conditions that may mitigate an immunodeficiency. Further, the heading for this section of Morozov et al at column 12, line 59 indicates that these conditions are to be treated by L-Glu-L-Trp, not by any combination therapy.

Column 20, line 50, as mentioned above, merely lists mesna in an extensive laundry list of “chemotherapeutic” agents. Other than this inclusion, mesna is not again so much as mentioned in the 156-column specification. Finally, Example 2, which begins at column 40 of Morozov, et al, describes the treatment of patients for radiation exposure at the Chernobyl nuclear plant accident site. Applicant’s review of this extensive example leads to the same conclusion as above, that only single agent therapy is taught by Morozov, et al. According to Example 2, Protocols A-E, all patients were treated for radiation exposure with single agent Thymalin for up to 3 years after exposure. L-Glu-L-Trp was administered as a single agent to 70 patients at 3 years post exposure in efforts to normalize their immune systems. At no point in the Example is there a suggestion, much less a teaching, of combination therapy with any other agent.

Considering the language of the instant claims, the Examiner’s reasoning that “Mesna is known in the art as a detoxifying agent,” is oversimplified. The instant claims call for a method of treating (Claims 1-4) or protecting (Claims 5-13) against adverse effects of radiation exposure. As pointed out in the instant specification, mesna is well known in the art as efficacious in protecting against unwanted side effects of certain chemical agents. Mesna is not

known-as a radiation protector, and while radiation and chemotherapy are both used at times to treat patients with cancer, they are entirely different forms of treatment, each with their own unique benefits and adverse effects. For example, a number of pharmaceutical (mesna, amifostine, etc.) and biopharmaceutical (various colony stimulating factors) protective agents are currently used to protect and to treat patients undergoing various forms of chemotherapy. Regarding radiation therapy, no effective treatment/protecting agents are currently known or used.

not claimed Even the treatment outlined in the Morozov et al reference does not teach or suggest the treatment of a patient for radiation damage. Morozov et al only teach a treatment compound and method to boost a patient's immune system, regardless of the underlying cause.

Therefore, Morozov et al do not teach a treatment/protection method for radiation exposure, rather they teach a treatment for one out of the many adverse effects of radiation exposure.

With regard to the Examiner's statement that the claims are open-ended and do not exclude the administration of other active agents (presumably because the word "comprising" was used), Applicant respectfully submits that this open-ended language is proper in this case. There is currently no medically accepted treatment/protection method, either single agent or combination, for radiation exposure that includes the administration of drugs as protective agents.

Favorable consideration is also solicited for new Claims 14 and 15, which specify the formula I compounds used in the methods as disulfides, alkylated mercaptans or conjugated amino acids. No teaching is shown in Morozov et al or any other reference of record to use such compounds for the treatment/protection of radiation exposure.

In conclusion, no *prima facie* case of obviousness has been established based on Morozov et al. 1) There is no suggestion to amplify Morozov's limited teaching of a method for stimulating a patient's immune system to the claimed method for treating/protecting a patient against radiation exposure; 2) there is no reasonable expectation that the method of Morozov et al would be successful in doing anything other than stimulating an immune response; and 3) even if Morozov could somehow be read to teach a method of treating/protecting against radiation exposure, Morozov et al fails because it does not teach or suggest all of the claim limitations, e.g., nowhere in Morozov does it teach or suggest what an effective amount of a formula I compound would entail.

Favorable reconsideration for all claims is respectfully solicited. Should the Examiner desire the need to communicate with the undersigned attorney, a newly issued direct dial number is noted below.

Respectfully submitted,



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